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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MCGARRY, SEAN	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 06/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/964,412	DE LA MONTE ET AL.	
	Examiner	Art Unit	
	Sean R McGarry	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 32-52 is/are pending in the application.

4a) Of the above claim(s) 43-52 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 35-42 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election without traverse of Group I, claims 35-42, in Papers filed 3/24/04 is acknowledged.

Claims 43-52 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Papers filed 3/24/04.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 35-42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The rejection below addresses the new claims and applicant arguments submitted 12/19/03.

The claimed invention is drawn to the treatment or prevention of dementias of Alzheimer's type of neuronal degeneration via the administration of antisense based nucleic acid based compounds. The antisense oligonucleotides correspond to a sequence of NTP mRNA defined by nucleotides 150-1139 of SEQ ID NO: 1.

The instant specification as filed provides only general guidance for antisense based drugs in treating disease. The specification provides general methodologies for determining effective sequences for the nucleic acid compounds used in the method and provides general methods for delivery of compounds in a treatment, for example (see pages 24-33). Example 8 of the specification shows that the recombinant over-expression of AD7c-NTP in cells in culture produces phenotypes associated with Alzheimer's disease neurodegeneration (see page 46, for example). It is noted, and quite important for one in the art to develop an antisense drug, that it is not clear what particular AD7c-NTP was used in the example since "AD7c-NTP" is defined by the instant specification to include variants (see page 17, for example).

The instant specification does not provide any specific guidance such as what particular antisense used effectively in the claimed method. The practitioner is left to perform trial and error experimentation to find antisense that may be an effective inhibitor that might be used in a method of treatment or prevention. The instant specification does not provide guidance or examples that would show by correlation what sequences of antisense based nucleic acid compounds of the method would predictably provide for treatment or prevention of disease in general or for the treatment of dementias of Alzheimer's type of neuronal degeneration specifically. The instant specification does not provide guidance or examples that would show by correlation what modes of delivery would predictable provide for a treatment of disease in general and for the treatment or prevention of dementias of Alzheimer's type of neuronal degeneration in particular. The specification, as asserted above provides general

methodologies where there is no specific guidance for one in the treatment or prevention of dementia in Alzheimer's type of neuronal degeneration. It is not taught, for example, how or when one in the art must begin a treatment regime in order to prevent dementia. How does one maintain antisense in target cells at a level, and at what level and for how long, such that dementia is prevented? The specification essentially presents many possible general methodologies but fails to indicate how any particular methodology would be appropriate for the specific disease to be treated. The specification does not, for example, provide guidance on how to deliver antisense to neuronal cells but asserts that one in the art only has to use/find/determine by trail and error experimentation, a means of delivery that will. This amounts to an invitation to find an appropriate method of delivery such that a treatment or prevention might be obtained. Would one in the art accept that a subcutaneous injection or transdermal administration would provide antisense to the brain such that dementia would be prevented? The instant specification does not provide any examples of inhibiting AD7c-NTP in cells in culture or in an animal or provide guidance that would show by correlation the treatment or prevention of dementias of Alzheimer's type of neuronal degeneration via the administration of antisense based nucleic acid compounds. The specification provides a system that may screen for compounds that may inhibit AD7c-NTP, but the specification has failed to provide one in the art a means to predictably make a nucleic acid based compound used in the claimed method of treatment or prevention such that no undue experimentation would be required in the making of the compound (ie selection of a predictable effective [in vivo] sequence) and further how to

deliver such a compound in a whole animal such that one would be able to treat or prevent dementias of Alzheimer's type of neuronal degeneration without undue trial and error experimentation.

The art of nucleic acid based therapies in an unpredictable art. Agrawal [TIBTECH, Vol. 14:376-387, October 1996] states the following: " [t]here are two crucial parameters in drug design: the first is the identification of an appropriate target in the disease process, and the second is finding an appropriate molecule that has specific recognition and affinity for the target, thereby interfering the disease process" (page376); "[o]ligonucleotide must be taken up by cells in order to be effective. [s]everal reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides {The instant specification fails to provide any guidance or examples that show an uptake of nucleic acid compound that would correlate to a predictable treatment of dementias of Alzheimer's type of neuronal degeneration , for example}. Cellular uptake of oligonucleotides is a complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum . . .[i]t is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency." (Page 378); "[m]icroinjection or using lipid carriers to supply an oligonucleotide in cell culture increases the potency of the oligonucleotide in cell culture, but it is not clear how relevant this approach is for *in vivo* situations." (Page379); "[a]ny antisense activity observed in such artificial systems [cell culture] should be scrutinized carefully with respect to the disease process and its applicability to *in vivo* situations."

(Page 379). The instant specification fails to consider the problems asserted above, for example. The specification fails to provide any particular guidance on how to deliver adequate oligonucleotides to a specified target cell such that there is a treatment or prevention of dementias of Alzheimer's type of neuronal degeneration.

Branch [TIBS Vol. 23, February 1998] addresses the unpredictability and the problems faced in the antisense art with the following statements: "[a]ntisense molecules and ribozymes capture the imagination with their promise or rational drug design and exquisite specificity. [h]owever, they are far more difficult to produce than was originally anticipated, and their ability to eliminate the function of a single gene has never been proven."; "[t]o minimize unwanted non-antisense effects, investigators are searching for antisense compounds and ribozymes whose targets sites are particularly vulnerable to attack. [t]his is a challenging quest."; "[h]owever, their unpredictability confounds research applications of nucleic acid reagents."; "[n]on-antisense effects are not the only impediments to rational antisense drug design. [t]he internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules."; "Years of investigation can be required to figure out what an 'antisense' molecule is actually doing,. . ."; "Because knowledge of their underlying mechanism is typically acting, non-antisense effects muddy the waters."; "because biologically active compounds generally have a variety of effects, dose-response curves are always needed to establish a compounds primary pharmacological identity. [a]ntisense compounds are no exception. [a]s is true of all pharmaceuticals, the value of a potential antisense drug can only be

judged after its intended clinical use is known, and quantitative information about its dose-response curve and therapeutic index is known."; [c]ompared to the dose response curves of conventional drugs, which typically span two to three orders of magnitude, those of antisense drugs, extend only across a narrow concentration range."; "[b]ecause it is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be determined empirically by screening large number of candidates for their ability to act inside cells."; "[b]inding is the rare exception rather than the rule, and antisense molecules are excluded from most complementary sites. [s]ince accessibility cannot be predicted, rational design of antisense molecules is not possible."; and, "[t]he relationship between accessibility to ODN binding and vulnerability to ODN-mediated antisense inhibition *in vivo* is beginning to be explored. . . [i]t is not yet clear whether *in vitro* screening techniques. . . will identify ODNs that are effective *in vivo*."

Jen et al [STEM CELLS Vol. 18:307-319, 2000] discuss antisense based therapy and the challenges that remain before the use of antisense becomes routine in a therapeutic setting. Jen et al discuss the advances made in the art but also indicate that progress needs to be made in the art. In the conclusion of their review Jen et al assert "[g]iven the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has remained elusive." It is also stated "[t]he key challenges to this field have been outlined above. [I]t is clear that they will have to be solved if this approach to specific antitumor therapy is to become a useful treatment approach. [a] large number of diverse and talented groups are working on this problem,

and we can all hope that their efforts will help lead to establishment of this promising form of therapy." It is clear from Jen et al that the state of the art of antisense is unpredictable and those highly skilled in the art are working towards making the art of antisense therapy more predictable but have many obstacles to overcome.

Applicant has asserted that at the time of filing, the mechanism by which antisense molecules function was well established. The art cited above and by applicant [Galderisi et al] would tend to challenge that assertion since all of the references clearly indicate that the mechanism of action is not clear-cut.

Applicant has cited Galderisi et al as evidence of enablement since the reference provides indications of successful therapeutic applications. First it is noted that neither the Galderisi et al reference nor any reference that the examiner is aware of provides evidence of prevention of any disease. If applicant is aware of such a reference it will be given full consideration upon submission. It has been asserted that the reference demonstrates that the reference shows that general techniques described by the reference [Galderisi et al] were available at the time of invention. It is noted that the Galderisi reference describes some specific methodologies using specific antisense oligonucleotides that have undergone extensive characterization and experimentation before their use in the treatments described. It is asserted that the reference provides evidence that general methodologies can be used in the treatment of any disease with antisense. It is noted that the Galderisi et al reference states "[t]he concept of antisense technology is simple. However, the development as broadly applicable therapeutic agents has been slow and difficult." (page 251) and, "[t]he use of antisense molecules

to modify gene expression is variable in its efficacy and reliability, raising objections about their use as therapeutic agents." (abstract) { these two statement indicate that, althought there has been some success, results are not predictable}, and, [w]hile the mechanism involved in cellular ODN uptake still is not clear, there is also great variation between different cell types with regard to their ability to internalize oligo molecules." (page 252) {has the instant specification taught a predictable method of delivering sufficient amounts of oligonucleotide to cells such that dementia will be treated or prevented?}, and assert at page 253 that the observed effects in the example of success that "these compounds may have some therapeutic efficacy likely through a combination of antisense and non-sequence dependent effects on gene function." Galderisi et al conclude with the assertion that "[t]he use of antisense to modify gene expression is variable in both efficacy and reliability, which caused objections about its use as a therapeutic agent. Most of these concerns can be overcome by the development of a new generation of antisense molecules with improved target specificity and enhanced delivery to the target cells." It does not appear that the instant application discloses a new generation of antisense oligonucleotides that overcome the unpredictability of the art and that general methodologies are insufficient in the use of antisense to treat any particular disease, for example. Applicant treatment of the references cited above do not obviate their evidence of unpredictability of the art. Applicant argues the Agrawal reference deal with the unpredictability of antisense in cells in culture, but it is noted that the instant specification fails to provide even cellular data, for example. Applicant asserts that the Branch reference teaches that non-

antisense effects might be advantageous, however, there has been no disclosure of or discussion of non-antisense in the instantly claimed invention being an advantage that overcomes the unpredictability of the art, for example. Applicant essentially argues, in the treatment of the cited references, that routine experimentation is all that would be needed. In view of that argued above and in view of the large volume of experimentation apparently needed to perform the claimed treatment or prevention of dementia via antisense it would appear to reach the level of undue experimentation since the specification only provided general guidance. Furthermore, the type of experimentation required to practice the invention more broadly than exemplified is a factor in the enablement analysis, but it not dispositive. In this case, the more or less standard nature of each type of experimentation required to expand the scope of an enabled invention is outweighed by the sheer quantity of experimentation to practice the full scope of the claims, the unpredictability of the art generally and the claimed method in particular, and the lack of guidance in the specification regarding the direction in which the experimentation should proceed.

One in the art would be required to engage in undue trial and error experimentation to practice the claimed invention since the specification as filed has failed to provide any particular sequences of the various antisense based compounds recited in the claim that would predictably be effective an effectively delivered to target cells in the treatment or prevention of dementias of Alzheimer's type of neuronal degeneration and also fails to provide with any particularity how one would specifically

treat or prevent dementias of Alzheimer's type of neuronal degeneration with antisense based nucleic acid compounds.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean R McGarry whose telephone number is (571) 272-0761. The examiner can normally be reached on M-Th (6:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SRM

SEAN McGARRY
PRIMARY EXAMINER
1635